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Review Article

MECHANISTIC ASPECTS OF LUMIKETONE PHOTO-REARRANGEMENT OF 4, 4-DISUBSTITUTED CYCLOHEXENONE SYSTEMS-A REVIEW

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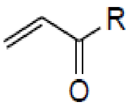
ABSTRACT

The photochemistry of α,β-unsaturated ketone is rich and varied with many facets of mechanistic interest. Cyclic α,β-enones, especially those with a six membered ring, undergo a number of photochemical reactions due to presence of energetically similar two triplet states 3(π,π*) and 3(n,π*). Among the different photoreactions of α,β-enones, Type A or Lumiketone rearrangement are very common in 4,4-disubstituted cyclohexenones. The mechanism of ketone-lumiketone rearrangement was a subject of extensive research for several years and both of the concerted and stepwise (radicaloid) mechanism has been discussed in detail in this review.

Keywords: α,β and β,γ-enones, photo rearrangement

1. INTRODUCTION

Enones are primarily of two types: conjugated and homoconjugated. The α,β-unsaturated enones (A) are the best examples of the conjugated enones while the β,γ-unsaturated enones (B) are homoconjugated one. Both of the enones, besides this individual chromophore-characteristic photoreactions, are characterized by specific rearrangement processes occurring because of the combination of 'ene' and 'one' part. The two characteristic photo rearrangements for α,β-enones like cyclohexenones are Lumiketone rearrangement (Type A) and Type B rearrangement [1]. Both of these rearrangements lead to ring contractions.



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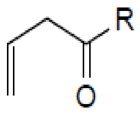


B

Besides α,β-unsaturated enones, the solution photochemistry of β,γ-unsaturated ketones has thoroughly been investigated and extensively reviewed in recent years [1-5]. It is characterized by two reactions: the allylic 1,3-acyl shift (1,3-AS) and the oxa-di-π-methane (ODPM) rearrangement [6].

2. PHOTOCHEMISTRY OF α, β-ENONES IN SOLUTION

The photochemistry of α,β-unsaturated ketone is rich and varied with many facets of mechanistic interest. Generally all acyclic and less rigid cyclic α,β-enones, on photoirradiation, relax rapidly by *cis-trans* interconversion and do not undergo intermolecular photochemical reactions. However, cyclic α,β-enones, especially those with a six membered ring, undergo a number of photochemical reactions, some of which are of considerable synthetic value. The lowest singlet state in α,β-enone has been characterized as $^1(n,\pi^*)$ [7]. This singlet state in general, undergoes rapid intersystem crossing (ISC) to a triplet state. Although ISC is spins forbidden, spin orbit coupling in α,β-enone let this triplet state to be formed with high efficiency [8]. Here again, among the two possible triplets, excitation energy of $^3(n,\pi^*)$ is localized in the carbonyl part, while for $^3(\pi,\pi^*)$ it is mainly localized at the α,β-alkene part (Fig.**1**). Unlike singlet state, it is a matter of debate to predict the ordering of energies between the two triplet states [9]. Ordering of these two triplet energies depend on reaction condition, polarity of the solvent used and/or the nature of substitution present in the compound [10].

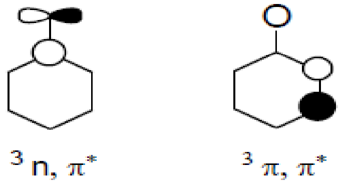
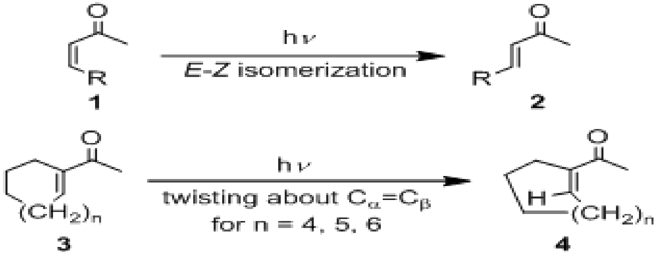


Fig.1: Two triplet energies of α,β-enone

The enone triplets have several reaction-pathways. In case of acyclic enones, triplets have generally have very short lifetimes due to their rapid deactivation through twisting about the $C_\alpha=C_\beta$ bond. Thus, for acyclic enones (**1**) *E-Z* isomerization is always the major reaction pathway from triplet states. Similarly triplets of medium sized ring enones like cycloheptenone and cyclooctenone are also short-lived and give an appreciable yield of stable or metastable ground state *trans*-enones through twisting of $C_\alpha=C_\beta$ bond upon decay from the π,π* triplet state. In case of cyclic enones (**3**), where the carbonyl group is exocyclic to the ring [11], such twisting very easily leads to the corresponding trans isomer (**4**) (Scheme **1**).



Scheme 1

Earlier it used to be thought that such bond twisting upon the deactivation of enone triplets in five or six membered ring enones cannot form ground state trans enones, because of increasing geometrical constraint around $C_\alpha=C_\beta$ bond. However, work of Yamauchi *et al.* has reported that relaxed 2-cyclopentenone triplet twist by about 40^0, 2-cyclohexenone triplet by 65^0, and acetyl cyclohexenone triplet by about 75^0 [12].

In solution phase, α,β-enones show a wide spectrum of different types of reaction (arising mainly from triplet excited states). Categorically they can be generalized into: (a) isomerization, (b) α and β-cleavage, (c) intramolecular H abstraction and photo-reduction, (d) photo-dimerization, (e) [2+2] Photocyclization, (f) photo-rearrangement etc. Among them, photo-rearrangement of cyclic α,β-enones like cyclohexenone and natural products containing cyclohexenone moiety like testosterenone acetate etc have been very widely studied and have been reviewed very well [1,13]. It has been found that for cyclic enones the two triplet states $^3(\pi,\pi^*)$ and $^3(n,\pi^*)$ are very close in energy. The $^3(\pi,\pi^*)$ minima is twisted in nature in non-rigid enone systems while the $^3(n,\pi^*)$ minima is planar one. Based on the reactivities of these two triplets, the photorearrangement for α,β-unsaturated cycloalkenones can be classified as follows:

a) Type A or Lumiketone rearrangement found in 4,4-disubstituted cyclohexenones.

b) Type B or 1,2-aryl or vinyl migration for 4,4-disubstituted cyclohexenones.

c) Other Rearrangements:

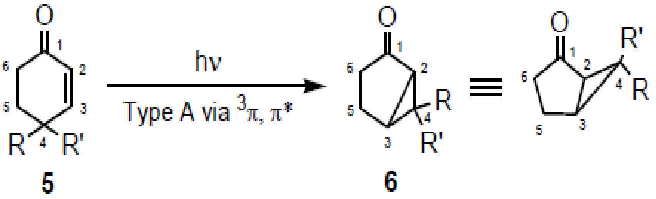
(i) Photo-Nazarov rearrangement originated from aroylcycloalkenones.

(ii) Type C for 5,5-disubstituted cyclohexenones.

(iii) Photorearrangement of 4, 4-diaryl-cyclohexadien-ones.

3. TYPE A (LUMIKETONE) REARRANGEMENT

4,4-dialkyl-2-cyclohexenones (**5**) on photoexcitation leads to ring-contraction to give bicyclo-[3.1.0]hexenones (**6**, Lumiketones), which involves the shift of the C(4)-C(5) bond to C(3) with concomitant formation of a new C(2)-C(4) bond (Scheme **2**).



Scheme 2

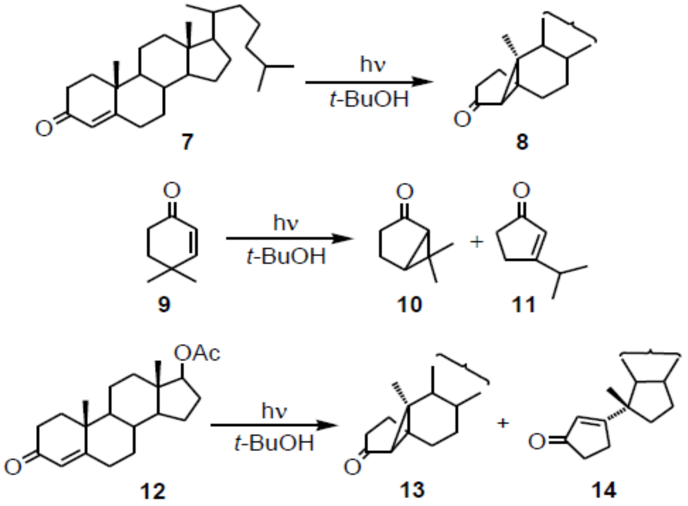
The reaction was first reported by Gardner and co-workers [14] in Δ^4- cholesten-3-one (**7**) and later by Chapman and co coworkers [15] on 4,4-dimethylcyclohex-2-en-1-one (**9**) and testosterone acetate (**12**) as shown below (Scheme **3**). However, the latter group also reported a ring contraction product (3-substituted cyclopent-2-en-1-one) along with the lumiketone rearranged product, when **9** and **12** were irradiated in presence of *t*-BuOH.

The characteristic features of Type A rearrangement are as follows:

i) The reaction proceeds via $^3(\pi,\pi^*)$ state.

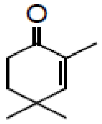
ii) The reaction pathway involves a twisting about the $C_\alpha=C_\beta$ bond in the triplet state which in turn forms a transient *trans*-isomers for cyclohexenone. This twisted triplet then decays largely to the ground state, accounting for the very low quantum yields of the

Type A or ketone-lumiketone rearrangement ($\Phi \sim 0.01$), but a small portion reacts to give the rearranged product – bicyclohexanone [1].



Scheme 3

iii) Generally, it was found that presence of two alkyl substituent at C-4 is a necessary (but not sufficient condition) for occurrence of this rearrangement [16] and some of the compounds **15**, **16**, **17** having the substituents at C-4 do not afford lumiketones since the twisting about the C_α=C_β bond is geometrically unfavourable in these cases.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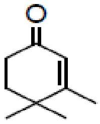
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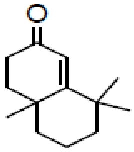
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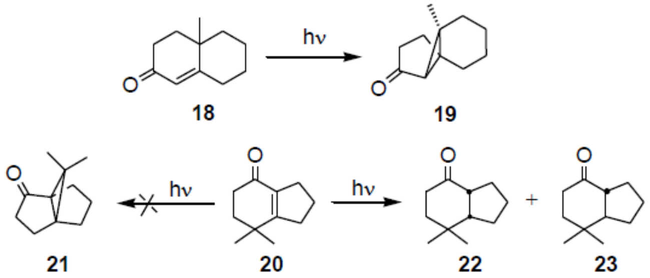
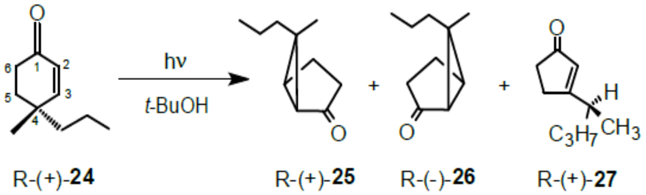
iv) Substitution pattern as well as twisting around C=C also controls this rearrangement. Thus while **18** gave the lumiketone rearranged product **19** [17] (Scheme **4**), **20** where the C=C is severely constrained to have a torsional motion around it, the rearrangement did not take place at all, (although quenching studies indicate the formation of reactive triplet state, probably $^3(\pi,\pi^*)$ [18].

v) The reaction needs polar solvents to occur. The yield of this rearrangement are usually optimal in *t*-BuOH, since in this medium the other possible and competitive side reaction like dimerization, reduction, deconjugation etc. are minimized.



Scheme 4

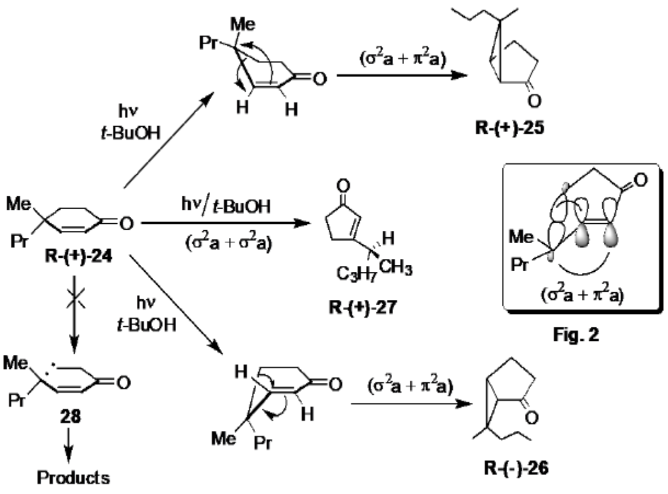
vi) The reaction is stereospecific with retention of configuration at C-5 and inversion of configuration at C-4. For example, Schuster and co-workers [17, 19] demonstrated that optically active enone (R)-(+)**-24** underwent photorearrangement on excitation in *t*-BuOH resulting in the formation of diastereomeric products **25** and **26** with inversion of configuration at C-4 (Scheme **5**).



Scheme 5

The mechanism of ketone-lumiketone rearrangement was a subject of extensive research for several years and both of the concerted and stepwise (radicaloid) mechanism has been proposed to predict its mechanism [1, 13]. However along with the above result (Scheme **5**), Schuster and co-workers also observed that there is no racemization of the starting material **24** during the 325 hr photolyzation. Hence, this observation ruled out the formation of an achiral ring opened diradical **28** in Type A rearrangement and suggested a concerted bond-switching mechanism, preferably (σ^2a + π^2a) cycloaddition process (Fig **2; under scheme 6**) during the formation of **25** and **26** and (σ^2a + σ^2a) for the formation of **27** from the triplet excited state of reactant **24** (Scheme **6**). Hence this mechanism can only invoke the inversion of configuration at C-(4) as the new σ bond is formed at the back lobe of the reacting C-(4) – C-(5) σ bond.

Apart from the above proposition, many attempts have been made to evaluate the nature of excited state involved in this rearrangement. However based on several experimental observations [17] carried out with different substituted 2-cyclohexenones, Schuster and co-workers proposed the actual mechanism with the help of the topology of T_1-S_0 potential surface of the Lumiketone rearrangement. According to them, a rapid ISC helps the enone S_1 to reach T_1 which then, depending on the structural variation of enone, relax energetically by twisting about the $C_\alpha = C_\beta$ bond as shown in fig **3** [17] . Calculation shows that this type of twisting always lowers the minima of $^3(\pi,\pi^*)$ energy. Consequently, this twisted triplet serves as an ideal geometry (or funnel) to cross directly to S_0, since, the energy minima (**P**) of T_1 excited surface is close to the energetically maxima (**Q**), which connects both of the enone-lumiketone ground state surface. However, since, the partition of the minima of T_1 lies more towards the enone (S_0) side, decay of T_1 to starting material becomes the major pathway rather than the minor formation of lumiketone. This then would explain the low quantum efficiency of this rearrangement.



Scheme 6

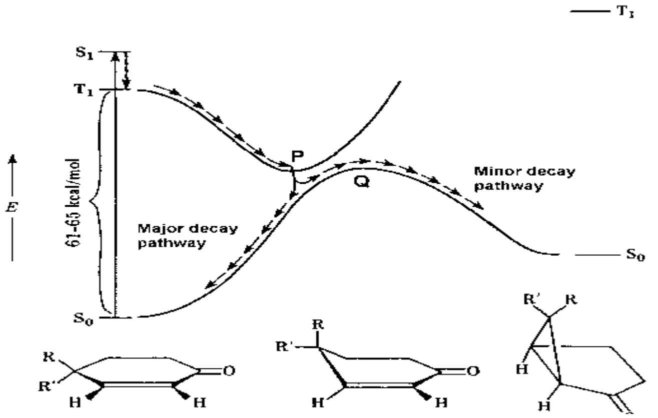


Fig. 3: Proposed potential Surfaces for the Lumiketone rearrangement of 4, 4'-dialkyl-2-cyclohexenones

However there was still an open question that whether the reaction follows excited state or ground state adiabatic pathway! From a theoretical model study of Type A rearrangement, Robb and co-workers [20] first showed that i) the reaction path goes through the twisted $^3(\pi,\pi^*)$ minima, ii) funnels for ISC may exist on both of the reactant and product side of the reaction pathway and iii) efficiency of ISC greatly depends on the rigidity of the enones and the nature of the solvent used.

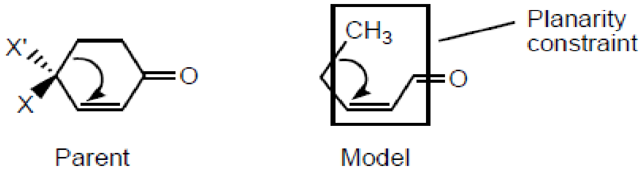


Fig. 4a: Lumiketone rearrangement model [20]

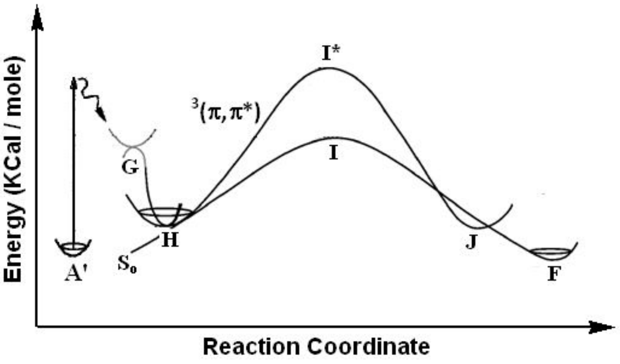


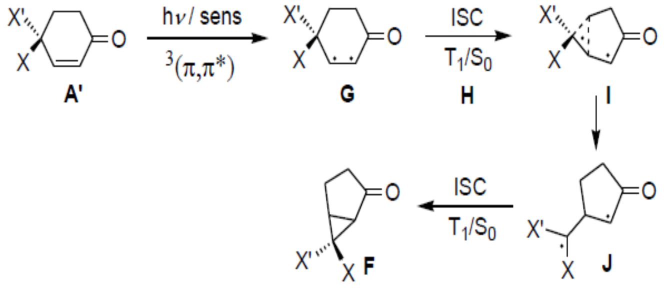
Fig. 4b: Schematic representation of the Lumiketone reaction pathway [20]

To avoid the complexity during the computational programme, the reaction pathway was modeled with rotationally constrained 2-(Z)-pentenal instead of 4,4'-disubstituted-2-cyclohexenones (Fig. **4a**). In this study, **G** has been found as the reference point in the excited state from where, in non-rigid enones twisting around the 'ene' $C_\alpha = C_\beta$ bond will bring the $^3(\pi,\pi^*)$ surface to a minima at **H** which touches $\mathbf{S_0}$ surface (Fig. **4b**). For the rigid enones, due to inhibition of twisting, **G** becomes minima and relaxation to **H** will be impossible. This explains non-occurrence of Lumiketone rearrangement for rigid enones. A very small spin-orbit coupling (SOC) for **H** to $\mathbf{S_0}$ intersystem crossing (ISC) makes it unfavorable. However in polar solvent SOC becomes larger and ISC- efficiency gets enhanced. This explains the role of polar solvent in Lumiketone rearrangement.

Now from **H**, the excited state migration via TS **I*** terminates at diradical minima **J**, where the $^3(\pi,\pi^*)$ surface is almost degenerated with $\mathbf{S_0}$. However, SOC at this point is almost zero. This fact along with a large excited state barrier rules out this $^3(\pi,\pi^*)$ route for lumiketone rearrangement. On the other hand, ground state migration path from **H** through TS **I** become favourable if ISC on the reactant side is made efficient by increasing the SOC, as observed when the reaction is carried out in polar solvent. Thus, Robb's work can only explain that the lumiketone rearrangement is a ground state adiabatic reaction, i.e, "funnel lies on the reactant side of the excited state reaction path and the photoexcitation process merely supplies the energy to overcome the ground state activation barrier" [20].

4. CONCLUSION

The Type A or Lumiketone rearrangement thus may be represented as Scheme **7**.



Scheme 7

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